The help of the district general manager, the director of public health, and members of the department of public health medicine, Central Nottinghamshire Health Authority, is gratefully acknowledged.

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(*Accepted 12 July 1991*)

Risk factors for developing non-insulin dependent diabetes: a 10 year follow up of men in Uppsala

Einar T Skarfors, K Ingemar Selinus, Hans O Lithell

Abstract

***Objective*—To analyse anthropometric and metabolic characteristics as risk factors for development of non-insulin dependent diabetes mellitus in middle aged normoglycaemic men.**

***Design*—Prospective population study based on data collected in a health survey and follow up 10 years later.**

***Setting*—Uppsala, a middle sized city in Sweden.**

***Subjects*—2322 men aged 47-53, of whom 1860 attended the follow up 7-14 years later, at which time they were aged 56-64.**

***Main outcome measures*—Incidence of non-insulin dependent diabetes.**

***Results*—In a multivariate logistic regression analysis, variations of 1 SD from the mean of the group that remained euglycaemic were used to calculate odds ratios and 95% confidence intervals. Blood glucose concentration 60 minutes after the start of an intravenous glucose tolerance test (odds ratio=5·93, 95% confidence interval 3·05 to 11·5), fasting serum insulin concentration (2·12, 1·54 to 2·93), acute insulin increment at an intravenous glucose tolerance test (1·71, 1·21 to 2·43), body mass index (1·41, 1·01 to 1·97), and systolic blood pressure (1·23, 0·97 to 1·56) were independent predictors of diabetes. In addition, the use of antihypertensive drugs at follow up (selective or unselective β blocking agents, thiazides, or hydralazine) was an independent risk factor (1·70, 1·11 to 2·60).**

***Conclusions*—Metabolic and anthropometric characteristics associated with or reflecting insulin resistance as well as a poor acute insulin response to glucose challenge were important predictors of future diabetes in middle aged men. Antihypertensive drugs were found to constitute a further, iatrogenic risk factor.**

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BMJ 1991;**303**:755-60

Introduction

That obesity is one of the predisposing factors for non-insulin dependent diabetes mellitus has been shown in several prospective population studies.[1-5] Hereditary factors as expressed by a history of diabetes in close relatives also seem to be important.[6-9]

During the past decade criteria for impaired glucose tolerance and non-insulin dependent diabetes have been set using the oral glucose tolerance test. In the early 1970s the intravenous glucose tolerance test seemed a likely tool for diagnosing diabetes, but no criteria for using it to diagnose non-insulin dependent diabetes have been proposed.

A low insulin concentration soon after glucose injection is found in normoglycaemic relatives of patients with non-insulin dependent diabetes and also in patients with impaired glucose tolerance or non-insulin dependent diabetes.[10,11] It has been suggested that people with a low early insulin response are at risk of developing non-insulin dependent diabetes,[12] but this has not been confirmed in prospective studies. Impaired insulin action (insulin resistance) is a precursor of non-insulin dependent diabetes in Pima Indians and Mexican-Americans[13-16] and white European women.[17]

During 1970-3 the intravenous glucose tolerance test was used in a large population based survey in Uppsala, Sweden, to characterise glucose metabolism in middle aged men. The present study aims to investigate the incidence of non-insulin dependent diabetes during an observation period of about 10 years in these men and

to find the risk factors for non-insulin dependent diabetes by using metabolic features, anthropometric measures, history of diabetes among relatives, and, especially, insulin concentrations at intravenous glucose tolerance test. Observations that diabetes is overrepresented among treated hypertensive men[18] and women[19] prompted us to evaluate hypertensive drugs as a risk factor for non-insulin dependent diabetes.

Methods

SUBJECTS

Between 1970 and 1973 the health of 2841 men born 1920-4 and resident in Uppsala was surveyed. In all, 2322 (81·7%) attended. The survey aimed to identify risk factors for cardiovascular disease in middle aged men and to select individuals at high risk for treatment,[20,21] and it used an intravenous glucose tolerance test to characterise the participants with regard to glucose metabolism and insulin values.[10,22]

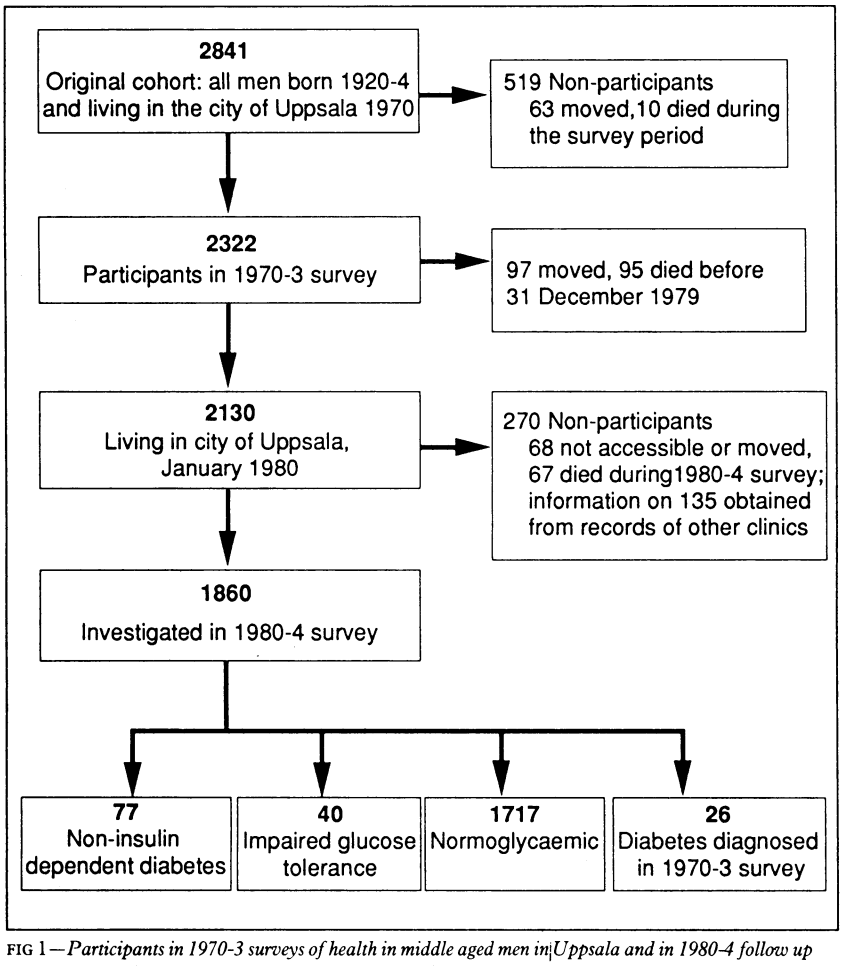

FIG 1—*Participants in 1970-3 surveys of health in middle aged men in Uppsala and in 1980-4 follow up*

We started to re-examine the eligible part of this cohort in January 1980. At that time 2130 men were still alive and registered as inhabitants of Uppsala. Sixty seven died before they had been investigated; of the remaining 2063, 1860 attended the second screening, giving an attendance rate of 90% (fig 1). Of the 270 initial participants who did not participate in the 1980 survey (but who were still living in Uppsala), 135 had regularly been checked by physicians. Requests for information about their fasting blood glucose, blood pressure, weight, and diagnosis were sent to their physicians.

Information about causes of death in the deceased men was supplied by the register of the National Statistics Office of Sweden. Information on diagnoses was not available at follow up in 165 (of whom 68 were resident in Uppsala) of the 2322 participants in the 1970-3 survey.

Routine investigative methods were used in a similar manner in the two surveys. The subjects were invited by letter and were asked to fast and to refrain from smoking from midnight before the investigation. A questionnaire was used in both surveys.[23] The questions concerning family history of diabetes mellitus, physical activity at work and during leisure time, smoking habits, and regular medication were identical in the two surveys. The number of siblings affected by diabetes was not specified on the questionnaire, but whether mother, father, both parents, or any siblings had diabetes could be determined.

GLUCOSE TOLERANCE TEST

An intravenous glucose tolerance test was performed in 1692 men (72·9% of those born 1921-4) in the 1970-3 survey.[20] For this test the subject lay supine after at least 15 minutes' rest. The glucose dose (0·5 g/kg body weight of a 50% solution) was given into an antecubital vein in about 2·5 minutes. Samples for determining blood glucose concentration were drawn before and 20, 30, 40, 50, and 60 minutes after the start of the glucose injection and were used for calculating the k value according to Ikkos and Luft.[24]

A glucose oxidase method (GOD-PERID, Boehringer Mannheim, Germany) and an LKB 7400 photometer were used for measuring glucose in whole blood in the 1980-4 survey and current routine methods (also on whole blood) were used in the 1970-3 survey.

A fasting blood glucose value was obtained in all participants in both investigations. If in the second survey this value was 5·7 mmol/l or higher an oral glucose tolerance test was performed one to two weeks later, at which 75 g glucose was given in 200 ml water. Glucose concentration was measured in venous whole blood before and 30, 60, 90, and 120 minutes after the ingestion of glucose. The National Diabetes Data Group citeria were applied to identify men who were diabetic.[25] Only one oral glucose tolerance test was performed in a total of 135 men.

To select normoglycaemic men, all subjects in the 1970-3 survey who had a fasting blood glucose concentration $\geq$6·7 mmol/l (120 mg/dl) and k value $\leq$0·9, as well as those taking drugs for diabetes, were excluded from all the statistical analyses.

SERUM INSULIN CONCENTRATIONS

The serum insulin concentrations during the intravenous glucose tolerance test were measured in duplicate in blood samples drawn before and 4, 6, 8, and 60 minutes after the start of the glucose injection. The average of the values at 4, 6, and 8 minutes are referred to as the peak insulin concentration and the difference between peak and fasting insulin concentrations is designated the insulin increment. Serum insulin was measured with the Phadebas insulin test (Pharmacia AB, Uppsala, Sweden).

ANTHROPOMETRIC MEASUREMENTS

Height (without shoes) was measured to the nearest centimetre and weight (in undershorts) to the nearest kilogram. Body fat was estimated by measuring skinfold thickness with a Harpenden calliper[26] to the nearest 0·2 mm at three different sites: on the dorsal aspect of the middle of the upper arm (triceps skinfold), just below the angle of the right scapula (scapular skinfold), and on the abdomen to the right of the umbilicus (abdominal skinfold). All measurements were made with the subject sitting. Measurements from the 1970-3 survey were used in this study.

SERUM LIPID CONCENTRATIONS

During 1980-4 serum cholesterol and triglyceride

concentrations were measured in a Technicon auto-analyser type II[27] both on samples from the second survey and on serum samples that had been stored in liquid nitrogen since 1970-3. The concentration of cholesterol in high density lipoprotein was assayed in the supernatant after very low and low density lipoproteins had been precipitated with a solution of heparin and manganese chloride.[28] Other blood analyses (serum urate, calcium, albumin, and phosphate concentrations) were performed by the methods in use at the time of the first survey at the department of clinical chemistry of the University Hospital, Uppsala.[20]

STATISTICS

A stepwise logistic regression program, BMDPLR, was used to test the importance of some variables that were univariately associated with the development of diabetes—namely, supine systolic and diastolic blood pressures, subscapular skinfold measurement, fasting glucose concentration and glucose concentration at 60 minutes, fasting insulin concentration and insulin concentration at 60 minutes, the k value of the intravenous glucose tolerance test, body mass index, insulin to glucose ratio (fasting and at 60 minutes), peak insulin value, insulin increment, serum triglyceride concentration, and family history for diabetes mellitus. Antihypertensive drugs being taken at follow up (β blockers, thiazides, and hydralazine) were also added.

The odds of an event is defined as $p/(1-p)$, where p is the probability of the event (the risk). The product $[p_1/(1-p_1)]\cdot[1-p_2)/p_2]$ is the odds ratio, where p_1 is the probability of developing diabetes when, for example, the subject has a supine systolic blood pressure equal to the mean and p_2 is the probability of developing diabetes when the subject has a blood pressure—1 SD from the mean. One SD was added to the mean when the normoglycaemic group had a lower mean than the group that developed diabetes and 1 SD was subtracted from the mean when the mean of the normoglycaemic group was higher. Default values for inclusion and exclusion of variables and for tolerance (0·15, 0·10, and 0·0001) were used in the BMDPLR program.[29] Interaction of pairs of risk factors was tested but did not yield significant results.

TABLE I—*Family history of diabetes and development of diabetes in middle aged Swedish men (10 years' observation)*

No of close relatives with diabetes	Total	No (%) developing diabetes
None	1488	51 (3·4)
1	251	17 (6·8)
2 or more	55	9 (16·4)
Total	1794	77

TABLE II—*Body mass index and incidence of diabetes in Swedish men*

Body mass index (kg/m²)	Total	No (%) with diabetes
≤22·99	496	7 (1·4)
23·00-	474	10 (2·1)
25·00-	427	15 (3·5)
27·00-	224	11 (4·9)
29·00-	107	14 (13·1)
≥31·00	66	20 (30·3)
Total	1794	77

TABLE III—*Baseline characteristics of men who remained normoglycaemic and those who developed diabetes*

Variable	Normoglycaemic	Developed diabetes	p Value (95% confidence interval) for difference between means
Mean (SD) blood glucose at 60 minutes (mmol/l)	10·9 (2·8) (n=1341)	15·6 (3·0) (n=50)	≤0·0001 (−5·5 to −3·9)
Mean (SD) fasting serum insulin (mU/l)	12·4 (6·9) (n=1354)	21·1 (11·9) (n=52)	≤0·0001 (−10·7 to −6·8)
Mean (SD) insulin increment (mU/l)	59·8 (47·6) (n=1262)	33·5 (35·1) (n=46)	≤0·0002 (12·4 to 40·2)
Mean (SD) body mass index (kg/m²)	24·73 (2·93) (n=1679)	28·57 (4·03) (n=69)	≤0·0001 (−4·6 to −3·1)
Mean (SD) systolic blood pressure (mm Hg)	131·6 (16·7) (n=1679)	144·6 (24·1) (n=69)	≤0·0001 (−17·2 to −8·9)
Mean (SD) insulin at 60 minutes (mU/l)	27·1 (17·1) (n=1350)	47·0 (21·8) (n=52)	≤0·0001 (−24·8 to −15·2)
Mean (SD) abdominal skinfold (mm)	19·5 (9·3) (n=1025)	28·4 (9·8) (n=32)	≤0·0001 (−12·1 to −5·5)
Mean (SD) heart rate (beats/min)	68·2 (10·3) (n=1679)	72·9 (10·8) (n=69)	<0·0002 (−7·2 to −2·2)
Mean (SD) diastolic blood pressure (mm Hg)	82·7 (10·5) (n=1679)	91·5 (12·9) (n=69)	<0·0001 (−11·4 to −6·3)
Mean (SD) serum triglycerides (mmol/l)	2·05 (1·14) (n=1679)	3·15 (2·15) (n=69)	≤0·0001 (−1·38 to −0·81)
Mean (SD) serum cholesterol (mmol/l)	6·47 (1·23) (n=1679)	6·72 (1·28) (n=69)	0·10 (−0·55 to 0·05)
Mean (SD) serum high density lipoprotein (mmol/l)	1·17 (0·32) (n=1367)	1·08 (0·26) (n=51)	0·047 (0·00 to 0·18)

Results

INCIDENCE OF NON-INSULIN DEPENDENT DIABETES

The mean observation time was 10·2 years (SD 1·3 (range 7·0-14·3) years). Seventy seven of the 1834 men who were normoglycaemic in the 1970-3 survey (4·2%) were found in the 1980-4 survey to have developed diabetes. This is close to the values reported previously in Swedish men.[3] However, the screening technique used in the present survey underestimates the frequency of diabetes and impaired glucose tolerance as some diabetic men may have a fasting blood glucose concentration <5·7 mmol/l. We identified only 40 subjects with impaired glucose tolerance, which is half the number expected with the prevalence of 4·3% found in the Swedish survey of men of similar age.[3] These 40 subjects were excluded from the statistical analyses.

Diagnoses of 202 of the 270 non-participants in the 1980-4 survey obtained from the records of other clinics or physicians or, in the case of the deceased, from the death register showed that 10 (5·0%) had developed clinical diabetes before the follow up.

Seventeen men (22%) with diabetes (diagnosed in the 1980-4 survey) were treated with sulphonylurea or biguanide; none were treated with insulin. Twenty nine (38%) were taking antihypertensive drugs. Thirty six (47%) were not aware of their metabolic aberration—that is, they replied negatively to the question "Do you have diabetes?" in the questionnaire. Fewer (31; 40%) knew that they were diabetic, and 10 (13%) stated that they did not know.

VARIABLES RELATED TO DIABETES

Table I shows that the incidence of diabetes increased from 3% in men who had no close relatives with diabetes to 16% in those with two or more. Among men who did not develop diabetes, 16·3% (280/1717) had a parent or sibling with the disease, compared with 33·8% (26/77) among those who did develop diabetes.

Table II shows that the incidence of diabetes increased from 1·4% to 30·3%—a factor of 22—from the lowest to the highest grouping for body mass index. Sixty of the 77 subjects who developed diabetes (79%) had a body mass index in the 1970-3 survey of ≥25·1 kg/m², which is classed as overweight[30] and also equalled the mean body mass index in the whole cohort. The most overweight group (body mass index ≥31·0 kg/m²) consisted of only 66 subjects (3·7% of the cohort) but accounted for almost a third of men with diabetes.

Table III compares anthropometric and metabolic data from the 1970-3 survey in men who in the 1980-4 survey had developed diabetes and those who had not. The body mass index was 16% higher, systolic blood pressure was 10% higher, fasting insulin concentration was 70% higher, blood glucose concentration at 60

minutes was 43% higher, and the insulin increment was 44% lower in the men who developed diabetes than in the men who remained normoglycaemic. Those who knew in the second survey that they were diabetic had lower k values for blood glucose (0·98 *v* 1·20, p<0·05) and lower concentrations of high density lipoprotein cholesterol (0·94 *v* 1·13 mmol/l, p<0·01) in the first survey than those who did not know that they were diabetic.

In the 1970-3 survey intravenous glucose tolerance tests were performed in 1692 subjects; 1364 participated in the 1980-4 survey, of whom 50 had developed diabetes. Few subjects with a high insulin increment developed diabetes, but this risk was five times higher for the quarter of the population with a low insulin increment (<30 mU/l) than for the quarter with a high insulin increment (>75 mU/l) (1·5% (5/327) *v* 8% (27/329), respectively).

Of all men with a low fasting insulin concentration (≤9·9 mU/l), 1% (6/564) developed diabetes. The corresponding figures for those in the medium (10·0-19·9 mU/l) and high fasting insulin (≥20·0 mU/l) ranges were 3·3% (20/615) and 15·2% (24/158), respectively. Men with low, medium, and high fasting insulin concentrations constituted 42%, 46%, and 12%, respectively, of all men for whom insulin data from the 1970-3 survey were available. Only 12% (6/50) of the men with diabetes had low fasting insulin concentrations; 44% had medium and 42% had high insulin values.

Figure 2 shows the effect of a combination of insulin increment and fasting insulin concentration on the risk for developing diabetes. With fasting insulin in the low or medium range the risk for diabetes was low, but the risk increased in the high insulin range, particularly if combined with an insulin increment in the medium or low range. The risk in the low insulin increment range was substantial, not only in the high but also in the medium range of fasting insulin.

In all, 325 patients (18·1% of the cohort) were taking antihypertensive drugs. Selective β blockers were used by 124 participants, non-selective β blockers by 155, thiazides by 192, and hydralazine by 46. Of the 77 diabetic subjects, 29 (38%) were taking antihypertensive drugs.

RISK FACTORS FOR DIABETES

A logistic regression analysis was performed to identify risk factors for diabetes. The variables included were insulin and glucose values from intravenous glucose tolerance test, anthropometric indices, blood pressures, serum lipid concentrations, use of antihypertensive drugs at follow up, and family history of diabetes. Glucose concentration at 60 minutes, fasting insulin concentration, insulin increment, body mass index, and systolic blood pressure were found to be independent risk factors, as was treatment with antihypertensive agents at follow up (table IV).

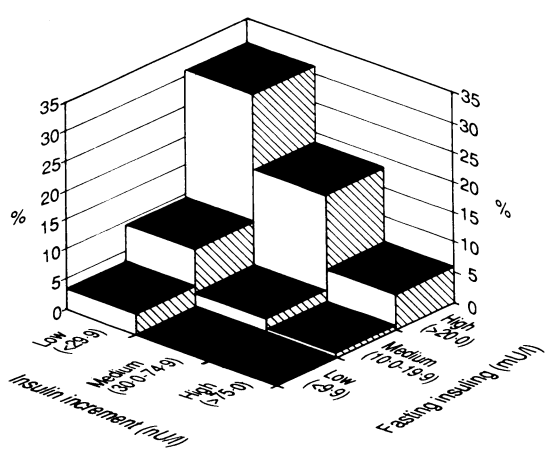

FIG 2—*Percentage of men with a combination of insulin increment and fasting insulin who developed diabetes*

TABLE IV—*Risk factors for development of diabetes*

Variable*	1 SD from the mean	Odds ratio (95% confidence interval)†	Model coefficient
Glucose at 60 minutes (mmol/l)	2·9	5·93 (3·05 to 11·5)	0·3810
Fasting insulin (mU/l)	7·7	2·12 (1·54 to 2·93)	0·0858
Insulin increment (mU/l)	−47·3‡	1·71 (1·21 to 2·43)	−0·0205
Body mass index (kg/m²)	3·09	1·41 (1·01 to 1·97)	0·0893
Systolic blood pressure (mm Hg)	17·4	1·23 (0·97 to 1·56)	0·0160
Taking antihypertensive drugs§	(No/yes)	1·70 (1·11 to 2·60)	0·0531

*Factors are presented in order of importance in the model.
†Calculated on 1 SD variation from the mean of the normoglycaemic group, except for antihypertensive drugs.
‡Normoglycaemic group had a higher mean value than the group that developed diabetes.
§Recorded at follow up.

One SD from the mean values of these variables (see table III) was used for calculation of odds ratios. The odds ratio for development of diabetes associated with a difference of 1 SD in glucose concentration at 60 minutes (2·9 mmol/l) was 5·93, and of 1 SD in fasting insulin concentration (7·7 mU/l) it was 2·12. The corresponding figure for insulin increment (−47·3 mU/l) was 1·71 (the minus sign indicates that the normoglycaemic group had a higher mean value for this variable than did the group that developed diabetes). Use of antihypertensive agents in the second survey versus no use had an odds ratio of 1·70, and a difference in systolic blood pressure (in the first survey) of 17·4 mm Hg had an odds ratio of 1·23.

The sensitivity was found to be 0·76 and the specificity 0·88 (calculated by use of variables as in table IV and by use of discriminant analysis).

When the risk factors associated with development of diabetes were combined the risk for an individual with risk factors corresponding to the mean values of the men who remained normoglycaemic (see table III) was 0·7%. A man with values of 1 SD from the normoglycaemic mean for glucose concentration at 60 minutes, insulin increment, body mass index, fasting insulin concentration, and systolic blood pressure had a risk of developing diabetes of 21%. Each risk estimate was significant except for systolic blood pressure (p>0·05). If treatment with antihypertensive drugs at follow up was added the total risk increased to 31%. When the use of antihypertensive drugs was added to the risk profile of a low risk subject the risk of developing diabetes increased from 0·7% to 1·2%.

Discussion

There have never been any widely accepted criteria for diagnosis of diabetes by use of the intravenous glucose tolerance test alone, and at the time of the first survey, 1970-3, the recommendations for interpretation of the oral glucose tolerance test were quite divergent. For this prospective study we used exclusion criteria based on the data from this test and fasting blood glucose concentration found in that survey to select a non-diabetic part of the cohort.[31] In the 1980-4 survey the criteria for non-insulin dependent diabetes mellitus proposed by the National Diabetes Data Group were applied to identify subjects who had developed diabetes during the observation period, but only subjects with a fasting blood glucose value ≥5·7 mmol/l were given an oral glucose tolerance test. This is likely to minimise the number of subjects with diabetes as a few men with a fasting blood glucose concentration >5·7 mmol/l might be diabetic by the group's criteria when given an oral glucose tolerance test. This would weaken the relation between the risk factors and diabetes.

The difference between the group that developed

diabetes and the group that remained euglycaemic was already clear at baseline. Those who developed diabetes had a higher body mass index and more pronounced central distribution of body fat, and concentrations of glucose at 60 minutes, fasting insulin concentration, and insulin concentration at 60 minutes were higher (by about 70%). Blood pressure and serum triglyceride concentrations were also significantly higher. Thus this group was characterised by all the classic features associated with insulin resistance (Reaven's syndrome X[32]): blood pressure is positively correlated with insulin concentrations (reflecting insulin resistance) and hypertension is an insulin resistant state in itself.[33,34]

Several mechanisms have been proposed to explain why raised insulin concentrations may lead to higher blood pressure.[35-37] Thus when blood pressure is found to be a risk factor for development of diabetes in the present study it may be regarded as an indicator of insulin resistance. Anthropometric data seemed to be less important in the present analysis than in an earlier report,[3] possibly because fasting or stimulated serum insulin concentrations are expressions of insulin resistance,[38-40] which in turn is related to body mass index or abdominal or subscapular skinfold thickness (as measures of central distribution of body fat). Therefore insulin concentrations, which increase in proportion to insulin insensitivity, were included in the statistical analysis whereas abdominal skinfold (a measure of central body fat distribution) was not, even though it probably constitutes much of the background of the insulin sensitivity. Nevertheless, obesity is probably the most important underlying preventable risk factor for diabetes, being to a large degree a consequence of lifestyle.

Men with first degree relatives with known diabetes were found to be at higher risk of developing diabetes than men with none, as has been found in other studies,[41] but a family history of diabetes was not an independent risk factor, which may reflect that insulin resistance or insulin increment, or both, are the risk factors that are inherited. When these factors were included in the statistical analysis heredity no longer contributed significantly, but this does not mean that heredity is not important.

At follow up 38% of the diabetic subjects were taking antihypertensive drugs, which reflects the increased risk run by treated hypertensive subjects of developing diabetes.[18,19,42] Diabetes has been reported to be more common in patients treated with diuretics and with propranolol. The treatment may confer a risk or hypertension in itself may be associated with an increased risk.[19] We found that treatment with any type of antihypertensive agent (diuretics, β blockers, or hydralazine) at follow up was an independent risk factor for developing diabetes.

We have recently shown in prospective trials that treatment with non-selective or selective β blockers as well as with diuretics is associated with an increased insulin resistance, resulting in increased concentrations of fasting insulin, insulin and glucose at 60 minutes, and a decreased insulin increment.[43,44] Those observations may explain the present finding of an increased risk during treatment with these drugs and accord with insulin resistance and low insulin increments being associated with an increased risk of developing diabetes.

In summary, in the present survey the men at high risk of later developing diabetes were characterised by several signs of insulin resistance. Obesity was the most important lifestyle feature related to subsequent manifestation of diabetes. Taking thiazides, both types of β blockers, or hydralazine at follow up was also significantly associated with developing diabetes. The present survey supports the view that antihypertensive drugs can precipitate diabetes in predisposed men. Long term antihypertensive treatment (as in this study) increases the odds of diabetes by a factor of about 1·7, independent of other risk factors.

This work was supported financially by the Swedish Medical Research Council (grant no 5446), the Swedish Physicians' Association, the Swedish Diabetes Association, the King Gustaf V Fund, and Uppsala University.

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(Accepted 4 July 1991)

Compulsive personality as predictor of response to serotoninergic antidepressants

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BMJ 1991;**303**:760-1

A large body of evidence suggests that serotoninergic antidepressants such as clomipramine, fluvoxamine, and fluoxetine are the most effective pharmacological treatments of obsessive-compulsive disorders.[1] The classic biochemical theory of major depression hypothesises disturbances in serotoninergic or catecholaminergic neurotransmission, or both. Until now, however, no specific symptoms have been clearly shown to orient with a selective antidepressant.[2] In addition to the depressive disorder, the underlying personality may be assessed as a possible aid to the therapeutic decision. Compulsive personality usually pre-exists in patients developing obsessive-compulsive disorder.[3]

We hypothesised that patients with a major depressive episode and an underlying compulsive personality would preferentially have serotoninergic depression and hence respond to a serotoninergic antidepressant such as fluvoxamine.[4]

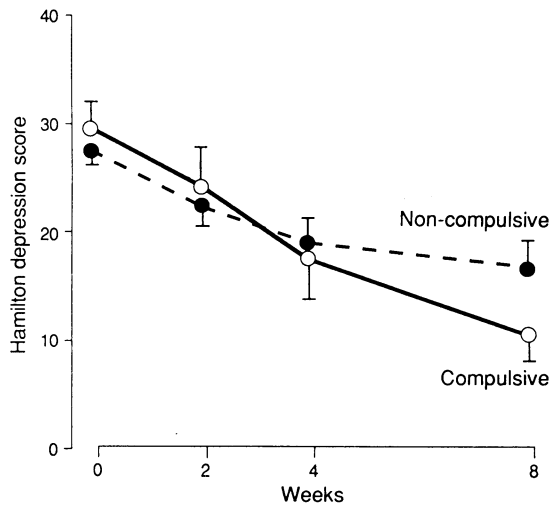
Patients, methods, and results

We studied 46 outpatients who fulfilled DSM-III criteria (*Diagnostic and Statistical Manual of Mental Disorders, Third Edition*) for a major depressive episode[3] and who also scored higher than 17 on the first 17 items of the Hamilton depression scale. The patients were among consecutive referrals to our department from general practitioners. Twenty two of the 46 patients had an underlying compulsive personality (DSM-III criteria)[3] as manifested by at least four of the following five features: restricted ability to express warm and tender emotions; perfectionism; insistence that others must submit to his or her way of doing things; excessive devotion to work and productivity; indecisiveness. The other 24 patients did not have a compulsive personality (only one or no compulsive feature).

The two study groups did not differ significantly in age (mean 46·8 years (range 28-63) *v* 41·3 years (22-64)), sex (12 men, 10 women *v* 12 men, 12 women), weight, duration of current depressive episode, previous treatment, medical or psychiatric history, or baseline level of depressive symptoms. The study lasted eight weeks and included assessments at baseline and after two, four, and eight weeks of treatment with the 24 item Hamilton depression scale and a subscale for endogenomorphic depression.[5] All side effects were recorded. The initial dose of fluvoxamine was 100 mg at bedtime, which could be increased to 200 mg from the third week. Other psychotropic drugs were excluded except for a low dose benzodiazepine anxiolytic or hypnotic, or both, if needed. The protocol was approved by the ethics committee of the university medical school and all patients gave informed consent.

Statistical analysis was by χ^2 test with the Yates correction for small samples, one way analysis of variance, and two way analysis of variance (compulsive *v* non-compulsive, four replications) with repeated measures. End point data in drop outs did not change the conclusions and are not reported.

Ten patients dropped out of the study because of lack of efficacy of the treatment or side effects (three patients in the compulsive group, seven in the non-compulsive group; $\chi^2=0{\cdot}84$, $p=0{\cdot}36$). To see whether completing the study could be prognostic an analysis of variance was performed on the basal Hamilton total score. This two way analysis (completer *v* non-completer, compulsive *v* non-compulsive) showed no significant effect or interaction. The same analysis of variance was performed on age, and this model also did not reach significance.



Changes over time in Hamilton depression scores with fluvoxamine in patients with major depressive episode with or without underlying compulsive personality. Bars are 95% confidence intervals

Comparison of changes in Hamilton depression scores over time showed significantly greater improvement in the compulsive group after eight weeks of treatment (F (3,32) = 10·65; $p=0{\cdot}0001$) (figure). This difference was even more pronounced on the subscale for endogenomorphic depression (F (3,32) = 7·09; $p=0{\cdot}0009$), which had already shown a significant difference between the groups after four weeks ($p=0{\cdot}05$). There was no significant difference between the groups in the number of reported side effects (mainly gastrointestinal; 12 patients in the compulsive group, 12 in the non-compulsive group; $\chi^2=0{\cdot}01$, df=1, $p=0{\cdot}92$). The mean final dose of fluvoxamine was 168·4 (SD 50·6) mg in the compulsive group and 179·4 (39·8) mg in the non-compulsive group ($F=0{\cdot}52$; $p=0{\cdot}48$).

Comment

These results suggest that depressive patients with an underlying compulsive personality respond better